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Risk factors associated with retinopathy of prematurity

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***Abstract*---**Background: Retinopathy of prematurity (ROP) is an important cause of preventable blindness in children. It is a serious and underestimated complication of prematurity treatment among preterm and low-birth weight babies and is preventable cause of blindness unless recognized and treated early. Objective: Evaluate the different neonatal risk factors for Retinopathy of Prematurity. Materials and Methods: A ROP prospective screening survey was performed enrolling all premature and low-birth-weight Neonates delivered at Index Medical College Hospital & Research Centre from July 2018 to June 2021, with a gestational age of 37 weeks or less at birth and a birth weight of 1700 g or less. One Hundred and Eighty Six (186) preterm infants (i.e.372 eyes) were included for ROP screening. Out of these 186 preterm infants (372eyes), Forty eight (48) preterm infants (i.e.96 eyes) developed Retinopathy of Prematurity. Descriptive statistics included the mean and standard deviation for numerical variables, and the percentage of different categories for categorical variables. Result: In our study, various risk factors are analysed for the disease Retinopathy of Prematurity. This statistical analysis is done by Chi-square test (P-value). Risk factors like Low Birth Weight, prematurity, Oxygen Therapy, hypoxia, blood transfusion, sepsis, mode of delivery, gestational age, multiple pregnancy, phototherapy has been analysed for their association with ROP.

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Keywords---low birth weight, prematurity, awareness, screening, retinopathy of prematurity, prevalence.

Introduction

Retinopathy of prematurity is a disease that occurs in premature infants and affects the blood vessels of the developing retina. It results in the development of vascular shunts, neovascularisation, and in its more severe forms, tractional retinal detachment. Retinopathy of prematurity (ROP) is an important cause of preventable blindness in children. It is believed to account for 6-18% of childhood blindness in developed countries[1,2]. In India, it has been estimated that 0.2% of childhood blindness is because of ROP. Of the 26 million children born each year in India, 7.8 million are low-birth-weight infants-1.68 million are less than 2500gms and 0.36 million are less than 1500gms and they are at risk of developing ROP[1,3].

The unique feature of ROP relates to its occurrence only in premature infants with immature and incompletely vascularised retina. ROP is mild and undergoes spontaneous regression with no visual sequelae in the majority of the affected infants. However, progression to advanced ROP does occur in a significant number of infants and can lead to severe visual impairment and even complete blindness in some infants. Thus, the most important factor in management of ROP is its early screening followed by proper management. In the absence of proper screening strategy, increasing number of premature infants who should have been successfully treated may turn irreversibly blind. This can lead to increase in social and economic burden of the society; especially in developing country like India, it can worsen the situation.

Retinopathy of prematurity was first described in 1942 by Terry[4]. He described an abnormal growth of fibroblastic tissue and blood vessels behind the lens, seen those days only in severe forms of ROP. This histological description led to the term Retrolental Fibroplasia (RLF).

Risk Factors Associated with Rop

Since the time ROP was first described, there have been numerous studies to identify the risk factors associated with the disease. The most consistent association has been found to be prematurity as reflected by low birth weight and gestational age. Many other factors implicated but definitive answer for cause relationship is awaited, and perhaps in the meantime the formula of **Avery** and **Glass** has some clinical sense[5].

Immaturity(always)+Oxygen(often)+Other factors(variably)=ROP

Other factors which have been studied are hyperoxia, hypoxia, hypercarbia, hypocarbia, metabolic acidosis, apnoea, respiratory distress syndrome (RDS) etc. Most of these factors have been found to be interdependent variables and on multiple regression logistic analysis, the association with ROP has been considerably weak.

Shohat et al (1983) examined 32 possible risk factors in 34 infants with ROP and noted that the following risk factors were significantly associated with ROP and noted the following risk factors were significantly associated with ROP: apnoea, blood transfusions and episodes of hypoxia and hypercarbia.[6]

Birth Weight and Gestational Age

The major ROP risk factor is the degree of immaturity as measured by either birth weight or gestational age. Although these two parameters are highly correlated, this is not variable as in IUGR. The incidence and severity of ROP are inversely related to birth weight and GA, the first being the most powerful predictor.[7]

Oxygen Therapy As A Risk Factor

Campbell et al in (1951) was the first to observe a possible relationship between ROP and oxygen exposure. She found that the lowest incidence of ROP in the hospital that used low oxygen in infants as supportive therapy.[8]

Patz et al[9], Ashton et al[10] and co-worker (1954) in a controlled study established that the overuse of oxygen was an important factor for the development of Retrolental Fibroplasia.

Kinsey et al in 1956 coordinated an 18 hospital collaborative study and published results confirming the role of oxygen in the development of ROP.[11,12]

Blood Transfusion As A Risk Factor:

Blood Transfusion is associated with ROP, this is explained by the theory that, transfusion of adult haemoglobin shifts the oxygen-haemoglobin dissociation curve to the right thereby releasing more oxygen to the tissues and leading to a state of relative retinal hyperoxia.
Lechner et al have (1997) suggested that changes in haematocrit and factors influencing blood flow are probably important influences than type of haemoglobin. [13]
Iron overloading theory also is related to ROP.[14]
Inder et al (1997) reported high erythrocyte transfusion in VLBW infants is associated with ROP.[15]
Hasse et al (1997) reported blood transfusion as a independent risk factor of ROP.[16]

Sepsis As A Risk Factor:

Aggarwal et al[17] (2002) and Vinekar et al[18] (2007) have also found that septicaemia is a risk factor for ROP. Sepsis may act through cytokines and end toxins, and is frequently accompanied by hypotension, which may impair tissue perfusion and release angiogenic factors secondary to hypoxic stress.

Light As A Risk Factor:

The exposure of retina to the bright light following premature birth has been suggested as a risk for ROP development, since the premature infants normally would be in dark, in utero environment.
Early exposure to light was suggested as a causative factor for ROP in the first description of this condition by Terry (1942).

The LIGHT-ROP study (1995-97) was designed to test the hypothesis that reducing the amount of light that reaches the eyes of preterm infants may be effective in preventing ROP. However, the **LIGHT-ROP** study demonstrated that there is no protective effect on ROP by limiting light exposure to new born premature infants.[19]

Multiple Pregnancies As A Risk Factor

R. Michael Siatkowski, Louis C. Blumenfeld, Rose Anne Johnson, John T. Flynn (Feb,1998) conducted a study to determine differences in incidence of retinopathy of prematurity between neonates of multiple-gestation and single-gestation pregnancies and to analyse differences in severity of retinopathy of prematurity among siblings of multiple-gestation pregnancies. The records of 149 neonates of multiple-gestation pregnancies and 691 single-gestation neonates screened for retinopathy of prematurity at one hospital from January 1, 1992, through December 31, 1995 were reviewed. The study concluded no significant difference in occurrence of ROP among infants of singleton pregnancies and infants of multiple pregnancies.[20]

Genes As A Risk Factor

Shastry et al (1997) were the first to suggest that genetic factor may play a role in the development of ROP. They suggested that some mutations may play a role for the development if Threshold ROP.[21]
In recent advances, some genes found to be associated with pathogenesis of ROP are **Norrie Disease** gene (ND) and of **VEGF**.
The importance of **VEGF** (1995) in the development of ROP is supported by a number of experimental and clinical data.[22]
Norrin (1998) is the product of the ND gene which plays a role in the angiogenesis.

Materials and Methods

This prospective study was conducted in Department of Ophthalmology and Department of Paediatrics, Index Medical College, Indore. Inclusion Criteria The study population included 186 neonates; preterm and low-birth weight babies of less than or equal to 1700 and/or grams and less than 37 weeks gestational age, born in Index Medical College Hospital& Research Centre, Indore, from July 2018 to June 2021 and admitted in the Neonatal Intensive Care Unit, Surviving at the post-natal age of 3 weeks, and Attending neonatal follow up clinic. Exclusion Criteria Infants born outside of this institute, with 1700 grams birth weight, and who fulfilled the inclusion criteria but did not survive till first eye examination for

Retinopathy of Prematurity (ROP). Gross 662 congenital malformations & lost during follow-up were excluded from this study. The parents were explained about the nature of the examination. Informed Parental consent regarding screening was taken.

Place

The place for the screening examination was a temperature controlled room, since premature neonates are susceptible to hypothermia. The screening was done in the presence of a neonatologist at Eye OPD so that any systemic complication can be handled easily. Those babies in incubators or on oxygen therapy were examined in the nursery with the ophthalmologist taking care to prevent contamination. The usual complications were bradycardia or a decrease in the oxygen saturation which was easily reversible. ROP screening examinations can have short-term effects on blood pressure, heart rate and respiratory function in the premature baby. The examinations was kept as short as possible and precautions were taken to ensure that emergency situations can be dealt with promptly and effectively. Eye examination during ROP screening may cause considerable pain to the neonate. A systematic review and meta-analysis comprising four studies has reported that oral sucrose reduces pain during eye examination.Of two studies reporting the role of topical proparacaine drops one has observed significant pain reduction. Discomfort to the baby was minimized by administering oral sucrose just before examination, pre-treatment of the eyes with a topical proparacaine and swaddling the baby. Baby was not fed just before examination to avoid vomiting and aspiration. Hand washing should be done and asepsis maintained.

Local eye examination

Pupils are dilated with Phenylephrine 2.5% and Tropicamide 0.5%. One drop of Tropicamide is instilled every 10-15 minutes for 4 times starting 1 hour before the scheduled time for examination.26 Screening for ROP was carefully done by indirect ophthalmic examination of the peripheral retina. Since the infant's eyes are small, a paediatric wire speculum was helpful in keeping the eyelids apart. Though Indirect Ophthalmoscopy was performed with a 20D lens, a 28D lens was helpful in examining the periphery especially in mid-dilated pupil.

• Descriptive statistics included the mean and standard deviation for numerical variables, and the percentage of different categories for categorical variables.

Result

Relation Of ROP To Birth Weight

In this study, 16 infants with ≤1250gms and 32 infants with >1250gms of birth weight, were having ROP of any stage. Whereas, 30 infants with ≤1500gms and 18 infants with >1500gms of birth weight, were having ROP of any stage. (ROP+)

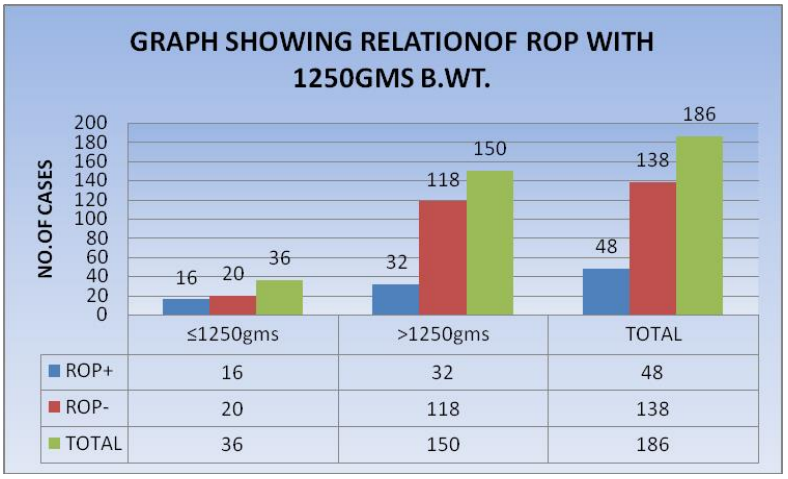

Fig. 1 Birth Weight ≤1250gms is strongly associated with ROP, as evident by high level of statistical significance (p value = 0.004) seen above. {p <0.05}

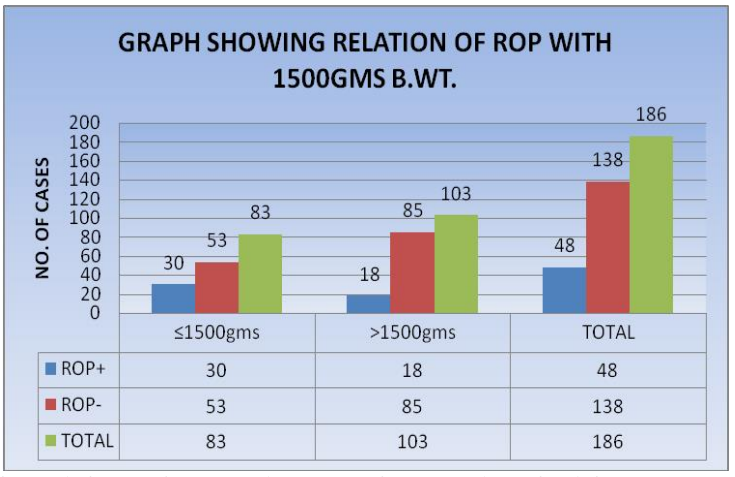

Fig. 2 Birth Weight ≤1500gms is strongly associated with ROP, as evident by higher level of statistical significance (p value= 0.004), as seen above. {p<0.05}

Relation Of ROP To Gestational Age:

In this study, 16 infants with ≤32 wks of gestational age and 32 infants with >37 wks of gestational age, were having ROP of any stage.

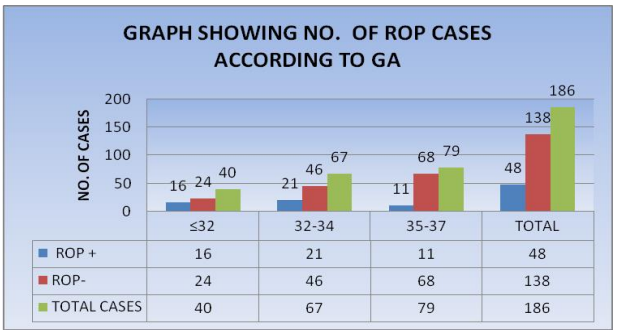

Fig. 3 Gestational age≤32 weeks is strongly associated with ROP, as evident by high level of statistical significance (p value=0.02), as seen above. {p< 0.05}

Relation Of ROP To Gender:

In this study, 25 infants were male and 23 infants were female, who were having ROP of any stage. (ROP+).

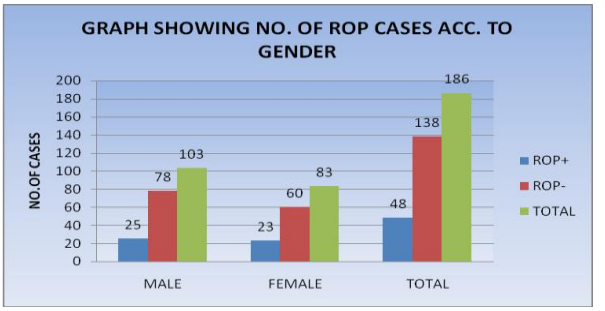

Fig. 4 There is no relation of ROP to male sex, as evident by low level of statistical significance (p value=0.59), as seen above. {p>0.05)

Relation Of ROP With Blood Transfusion

In this study, 16 infants who received blood transfusion and 32 who did not receive any blood transfusion were having ROP of any stage. (ROP +).

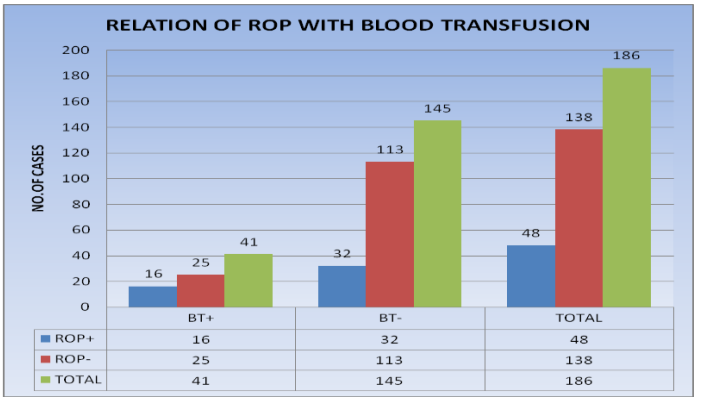

Fig. 5 Blood Transfusion is strongly associated with ROP, as evident by high level of statistical significance (p value=0.03), as seen above. {p<0.05}

Relation Of ROP With Sepsis

In this study, 16 infants with sepsis and 32 infants without sepsis were having ROP of any stage. (ROP+)

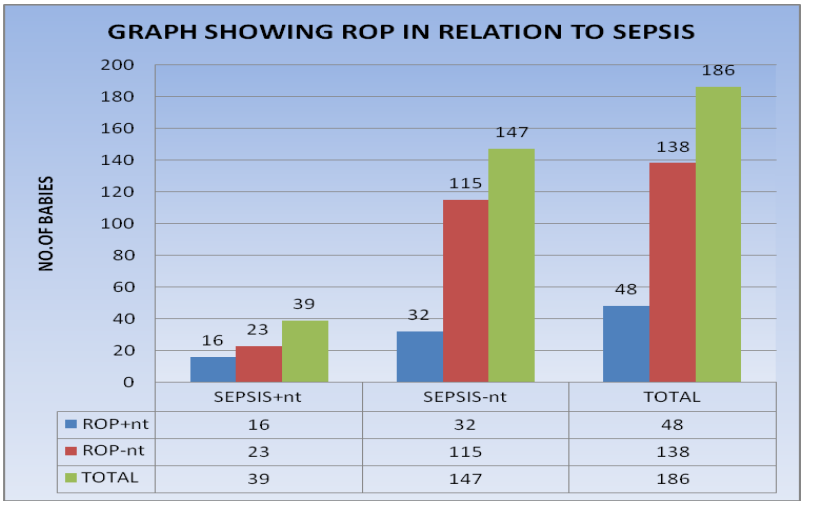

Fig. 6 Sepsis is strongly associated with ROP, as evident by high level of statistical significance (p value=0.01), as seen above. {p<0.05}

Relation Of ROP With Hypoxic/Apneic Attacks

In this study, 5 infants with apneic attacks and 33 infants with no apneic attacks, were having ROP of any stage.

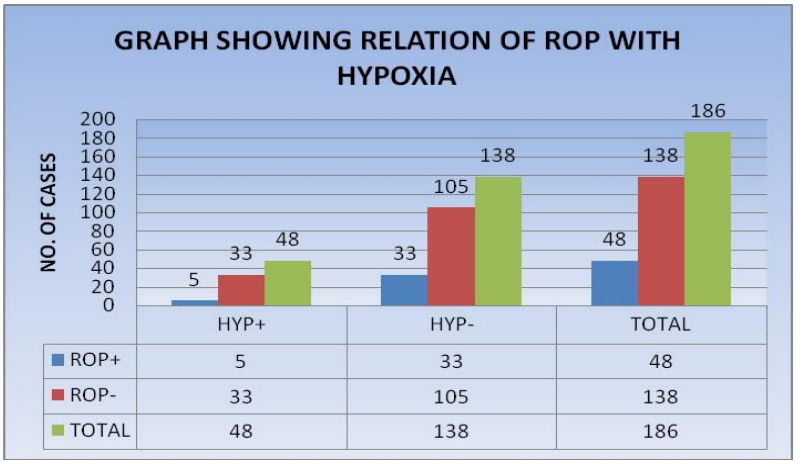

Fig. 7 Apneic or hypoxic attacks are strongly associated with ROP, as evident by high level of statistical significance (p value=0.03), as seen above. {p<0.05}

Relation Of ROP To Multiple Pregnancies:

In this study, 9 infants were product of multiple pregnancies, and 39 infants were products of singleton pregnancy, who were having ROP of any stage. (ROP+)

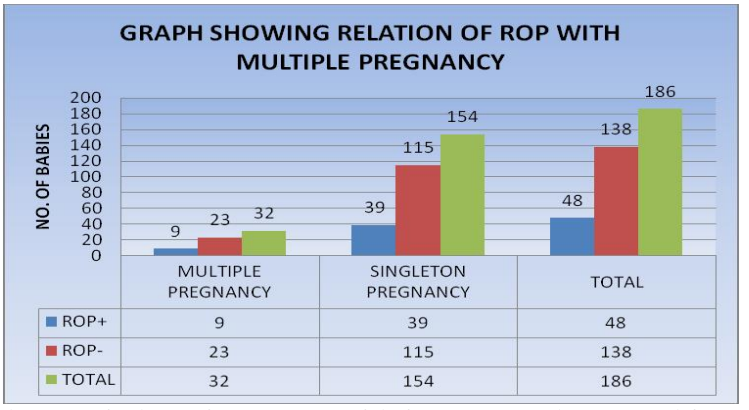

Fig. 8 There is no relation of ROP to multiple pregnancies, as evident by low level of statistical significance (p value=0.741), as seen above. {p>0.05}

Relation Of ROP With Mode Of Delivery

In this study,26 infants were delivered by LSCS, 22infants were delivered by NVD, and having ROP of any stage. (ROP+)

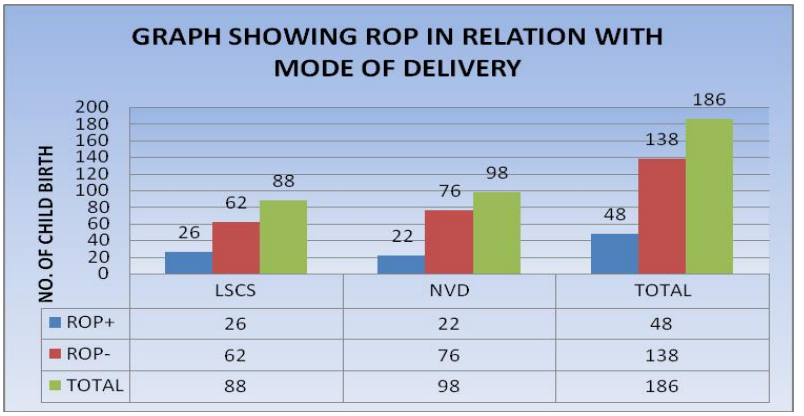

Fig. 9 There is no relation of ROP to mode of delivery, as evident by low level of statistical significance (p value=0.21), as seen above. {p>0.05}

Relation Of ROP With Phototherapy

In this study, 22 infants received phototherapy, 26 infants did not receive phototherapy, were having ROP of any stage. (ROP+)

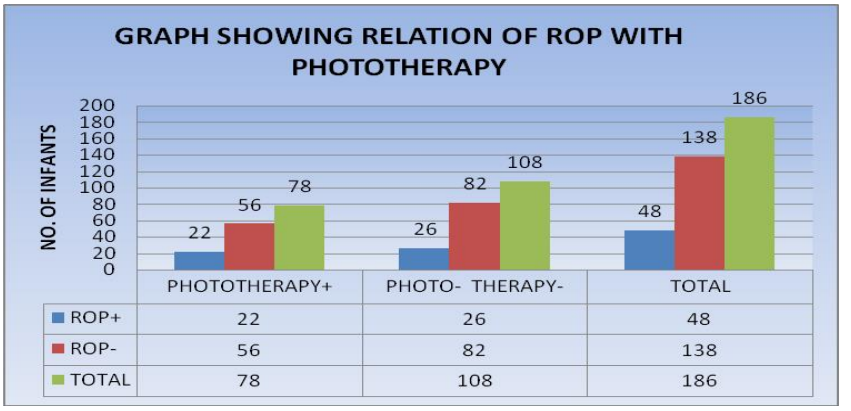

Fig. 10 There is no relation of ROP to phototherapy, as evident by low level of statistical significance (p value=0.52), as seen above. {p>0.05}

ROP In Relation To Oxygen Therapy

In this study, 20 infants received oxygen therapy, 28 infants did not receive oxygen therapy, and were having ROP of any stage. (ROP+)

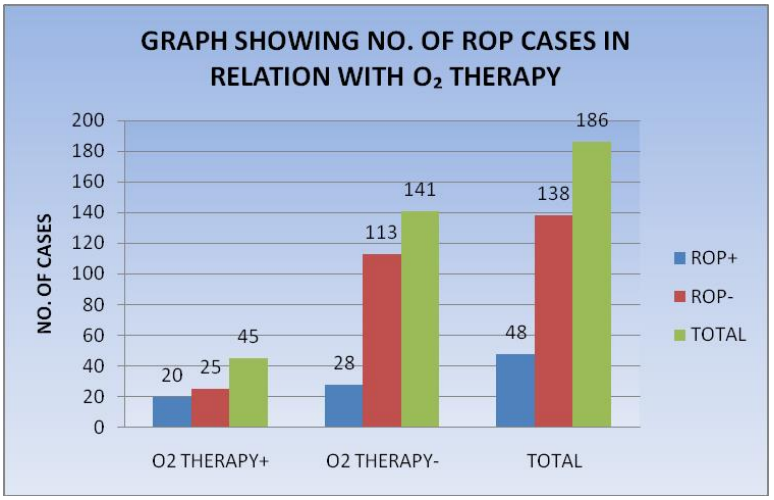

Fig. 11 Oxygen therapy is strongly associated with ROP, as evident by high level of statistical significance (pvalue=0.001), as seen above. {p<0.05}

Table Different Risk Factors With P-Value ODD' S ratio, log or and 95%CI Results

S.NO. S.NO.	RISK FACTORS	ROP (N=48)	NOROP (N=138)	P value	ODD'S ratio (OR)	LOG OR	95%CI	significance level
1	Birth Weight ≤1250gms	16(33.33%)	20(14.50)	0.004	2.95	0.4698	0.74-3.43	SIGNIFICANT
2	Birth Weight ≤1500gms	30(62.50%)	53(38.41)	0.004(0.0038)	2.67	0.4265	0.78-3.01	SIGNIFICANT
3	Male	25(52.08%)	78(56.52%)	0.6(0.59)	0.836	-0.0778	0.48-1.80	INSIGNIFICANT
4	Gestational Age≤32wks	16(33.33%)	24(17.40%)	0.02	2.37	0.3747	0.70-3.06	SIGNIFICANT
5	Blood Transfusion	16(33.33%)	25(18.12%)	0.03(0.028)	2.26	0.3541	0.67-2.98	SIGNIFICANT
6	Sepsis	16(33.33%)	23(16.67)	0.02(0.0145)	2.5	0.3979	0.70-3.15	SIGNIFICANT
7	Oxygen Therapy	20(41.67%)	25(18.12%)	0.001	3.22	0.5079	0.56-4.93	SIGNIFICANT
8	Multiple Pregnancy	9(18.75%)	23(16.67%)	0.741	0.96	-0.0177	0.42-2.30	INSIGNIFICANT
9	Mode of Delivery (LSCS)	26(54.17%)	62(44.93%)	0.21	1.448	0.161	0.61-2.27	INSIGNIFICANT
10	Apneic Attacks	5(10.42%)	33(23.91%)	0.03(0.028)	0.482	-0.317	0.26-2.02	SIGNIFICANT
11	Phototherapy	20(41.67%)	58(42.03%)	0.524	1.239	0.2143	0.64-2.40	INSIGNIFICANT

Risk Factors

In our study, various risk factors are analyzed for the disease Retinopathy of Prematurity. This statistical analysis is done by Chi-square test (P-value). Risk factors like Low Birth Weight, prematurity, Oxygen Therapy, hypoxia, blood transfusion, sepsis, mode of delivery, gestational age, multiple pregnancy, phototherapy has been analyzed for their association with ROP.

Birth Weight

In our study, infants, both with birth weight ≤1250gms and ≤1500gms were analyzed for association of Low Birth Weight with ROP. Birth Weight with ≤1250gms showed strong association with ROP with P value =0.004(P<0.05) (as in table). Birth weight with ≤1500gms also showed significant association with the disease with P value=0.003(P<0.05) (as in table). The mean birth weight of cases with ROP in our study was 1388±243gms.

This association can be explained by the fact that low birth weight babies undergoes a large number of problems related to prematurity, which leads to increase in the exposure of the babies to supplementary oxygen therapy. Increase exposure of the oxygen in premature infants leads to the immature retina in them to develop ROP.
This is in accordance with other studies mentioned in review of literature.[7]

Gestational Age

In our study, infants with gestational age ≤32wks was strongly associated with ROP, with a P value=0.02. This association is again due to the fact that low gestational age leads to low birth weight which leads to the problem of immaturity in them. Supplementary oxygen in such infants causes ROP in them.
This again is in accordance to the studies of review of literature.[7]

Supplementary Oxygen Therapy

Our study shows a strong relation between infants exposed to supplementary oxygen therapy to that with the development of ROP, with a P-value=0.001. This result can be explained by the fact that most of the infants in our study are preterm and critically ill. So as a part of line of treatment of such infants, supplementary oxygen is given which leads to ROP, which has been explained earlier according to pathogenesis of ROP and is in accordance to studies of literature.[8,9,10,12]

Sepsis

A significant association was seen between the disease and the infants with a P value=.01. This can be explained by the fact that sepsis is associated with mostly all terminally ill infants. Such infants are mostly associated with risk such as low birth weight, small gestational age and oxygen therapy which leads to increase in ROP in such infants.
This is comparable to studies in review of literature.[17,18]

Blood Transfusion

In our study blood transfusion is strongly associated with Retinopathy of Prematurity with a P value=0.02. Critically ill preterm infants mostly are associated with multi-organ dysfunction, bleeding, etc. To prevent above mentioned problems and stop bleeding in vital organs, blood transfusion is mandatory.
This is comparable to the results of studies in review of literature.[13,14,15,16]

Apnea/ Hypoxia

Our patients with ROP had a significant higher association with ROP, with P-value=0.027(0.03), which is in agreement with other studies. This can be explained by hypoxemia, fluctuating, level of oxygen and hyperoxemia following therapy for apnoea.
This is in accordance to the studies in review of literature.[6]

Insignificant Risk Factors

A further analysis of the purported risk factors revealed that – Gender, Multiple pregnancy, Mode of delivery, phototherapy were statistically insignificant risk factors. P value=0.59(0.60) for gender,0.7 for multiple pregnancy,0.21 for mode of delivery,0.524for phototherapy all of which are >0.05, showing statistical insignificance.

Conclusion

The different risk factors with ROP in our study are as follows:

Significant Risk Factors:

- Birth weight≤1250gms
- Birth Weight≤1500gms
- Gestational age<32wks
- Sepsis
- Apneic/Hypoxic attacks
- Blood Transfusions
- Oxygen Therapy

Insignificant Risk Factors:

- Mode of Delivery
- Male sex
- Multiple Pregnancies
- Phototherapy

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